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Total syntheses of the highly potent anti-cancer polyacetylenes, (*S*)-18-hydroxyminquartynoic acid, (*S*)-minquartynoic acid and (*E*)-15,16-dihydrominquartynoic acid ☆

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Abstract—The total syntheses of three polyacetylenic natural products, (*S*)-18-hydroxyminquartynoic acid (**1**), (*S*)-minquartynoic acid (**2**) and (*E*)-15,16-dihydrominquartynoic acid (**3**), has been achieved. The Cadiot–Chodkiewicz cross-coupling reaction was used as the key step for the construction of tetrayne and triyne units.

Naturally occurring polyacetylenes are an intriguing class of natural products.[1] Many of them show remarkable biological activities, such as antifungal, antimicrobial, cytotoxic, antiviral, antitumor, immunosuppressant and enzyme-inhibition.[2] Recently, there has been an increasing interest towards the synthetic studies of natural acetylenic compounds.[3] Three novel polyacetylenic compounds (*S*)-18-hydroxyminquartynoic acid (**1**), (*S*)-(−)-minquartynoic acid (**2**) and (*E*)-15,16-dihydrominquartynoic acid (**3**) were isolated from a chloroform extract of the twigs of *Ochanostachys amentacea* from south east Asia.[4] (*S*)-(−)-Minquartynoic acid was previously isolated from the stem bark of *Minquartia guianensis*,[5] which was one of the most potent traditional anthelmintics used by the Quijos Quichua people of Ecuador's Amazonian low lands. All three compounds showed potent cytotoxicity against ten different tumor cell lines,[5] while compound **3** showed the most potent activity among the three polyacetylenes against the human hormone-dependent prostate and ovarian cancer cell lines. Anti-HIV activity of **2** was also reported by two other groups.[6] The reported structure of **2** was revised based on HMQC and HMBC experiments, and the absolute stereochemistry was determined by Mosher's ester methodology.[4,7] The structures of compounds **1** and **3** were elucidated using 1D- and 2D-NMR spectroscopic methods. Compound **1** is (*S*)-17,18-dihydroxy-9,11,13,15-octadecatetraynoic acid, minquartynoic acid (**2**) is (*S*)-17-hydroxy-9,11,13,15-octadecatetraynoic acid, and **3** is (*S*)-17-hydroxy-15*E*-octadecen-9,11,13-triynoic acid. Reports by Gung et al. have described[8–10] the first total syntheses of these polyacetylenes. The draw back of the reported procedures is the isolation of a mixture of three possible acetylenic products when a key step, one-pot, three-component coupling strategy was employed, which reduced the yield of the desired cross-coupling product. Fascinated by the structures of these polyacetylenes, together with their remarkable anti-cancer activities, and as a part of our efforts towards the total synthesis of polyacetylenic alcohols,[11] we became interested in the total synthesis of **1**–**3** using a Cadiot–Chodkiewicz cross-coupling reaction[12] as the key step.

Our retrosynthetic analysis for **1**–**3** is outlined in Scheme 1. We envisioned that both polyacetylenes **1** and **2** could be constructed from the Cadiot–Chodkiewicz cross-coupling reaction of polyacetylenic alcohol **4** and bromodiyne **6**. Following a common strategy, **3** could be conveniently synthesized by coupling hydroxy enyne **7** with the bromodiyne **6**.

The syntheses of (*S*)-17-hydroxy-9,11,13,15-octadecatetraynoic acid (**1**) and (*S*)-(−)-minquartynoic acid (**2**) were started by preparing the chiral diacetylenic alcohol

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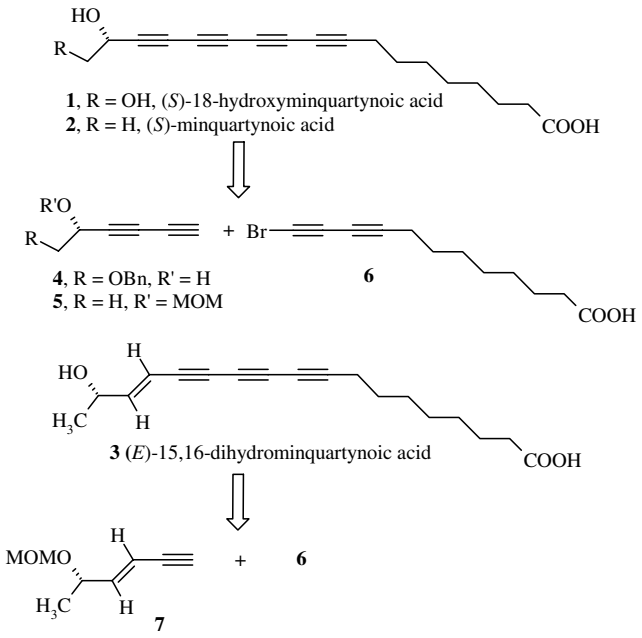
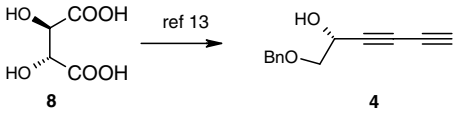


Scheme 1. Retrosynthetic analysis.

4 from L-(+)-tartatic acid **8** using the procedure developed by our group (Scheme 2).[13]

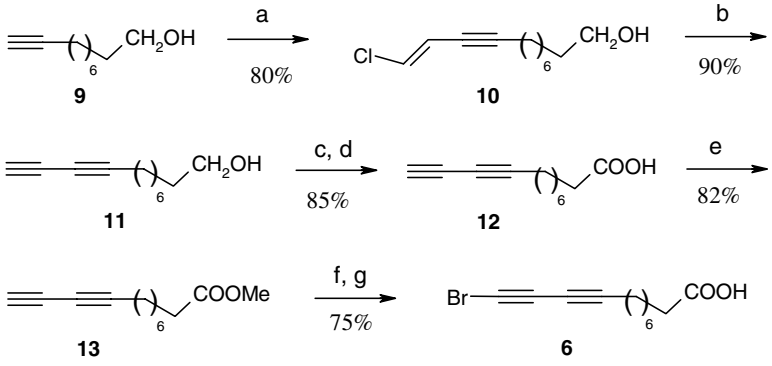


Scheme 2.

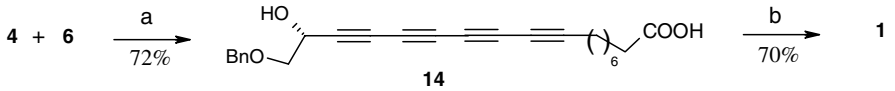
The right-hand fragment, bromodiyne **6**, was prepared as shown in Scheme 3. Accordingly, the cross-coupling reaction of **9** with *trans*-1,2-dichloroethylene under modified Sonogashira conditions[14] proceeded to afford **10** in good yield, which was subsequently treated with *n*-BuLi to produce terminal diyne **11**. Oxidation under Swern conditions, followed by treatment with $NaClO_2$:NaH_2PO_4 (1.5:0.2 equiv) in DMSO, furnished the corresponding carboxylic acid **12**. Esterification of **12** was accomplished by treatment with CH_2N_2 to afford methyl ester **13**. Finally, bromination of diyne **13** to give bromodiyne **6** was achieved in two steps in excellent yield by reaction with NBS and $AgNO_3$ in acetone,[15] followed by hydrolysis with LiOH (Scheme 3).

With bromodiyne **6** and alcohol **4** in hand, coupling via the Cadiot–Chodkiewicz reaction[12] produced the corresponding tetrayne **14** in 72% yield. Removal of the benzyl group using $TiCl_4$ at 0 °C to rt in DCM afforded the target molecule, (*S*)-18-hydroxyminquartynoic acid (**1**) in 70% yield (Scheme 4). The synthetic material **1** was identical in all respects with the natural product.

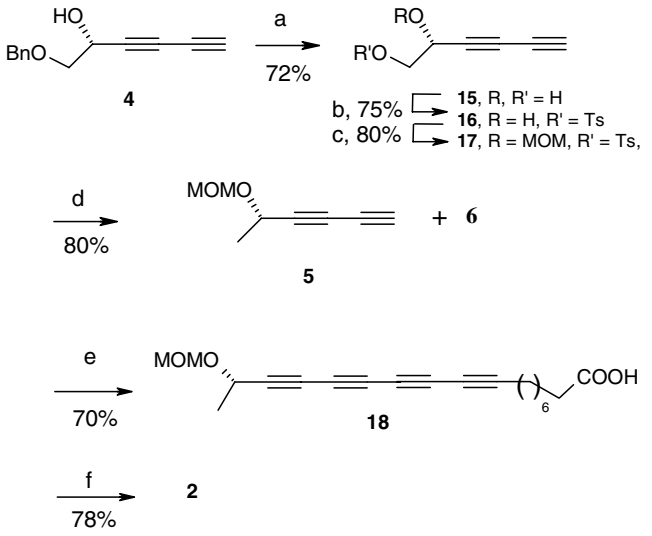
The synthesis of **2** also began with the known chiral diacetylenic alcohol **4** by manipulating the following reactions successfully (Scheme 5). The benzyl group in **4** was removed with $TiCl_4$ in DCM, and the resulting diol **15** was selectively tosylated by treatment with tosyl chloride in pyridine at 0 °C to furnish the corresponding tosylate **16** in 75% yield. After protecting the secondary hydroxy group of compound **16** as its MOM ether, the tosyl group of **17** was reduced to a methyl by treatment with LAH in dry ether at room temperature to afford compound **5**. Adopting the same strategy as for the synthesis of **1**, the coupling of **5** with bromodiyne **6** under Cadiot–Chodkiewicz conditions resulted in tetrayne **18**



Scheme 3. Reagents and conditions: (a) *trans*-1,2-dichloroethylene (1 equiv), $Pd(PPh_3)_4$, Et_2NH (2 equiv), CuI (0.2 equiv), toluene, 30 min; (b) *n*-BuLi/HMPA (1:1 equiv), −40 °C, 30 min; (c) $(COCl)_2$, DMSO, TEA, −78 °C, 1 h; (d) $NaClO_2/NaH_2PO_4$ (1.5:0.2 equiv), DMSO, 1 h; (e) CH_2N_2, ether, 0 °C, 30 min; (f) NBS, $AgNO_3$, acetone, 0 °C to rt, 20 min; (g) LiOH (1 equiv), THF/MeOH/H_2O (3:1:1), 40 min.



Scheme 4. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$ (1 equiv), $EtNH_2$ (1 equiv), CuCl (0.2 equiv), MeOH (5 ml), H_2O, 20 min; (b) $TiCl_4$ (0.01 equiv), DCM, 0 °C to rt, 2 h.



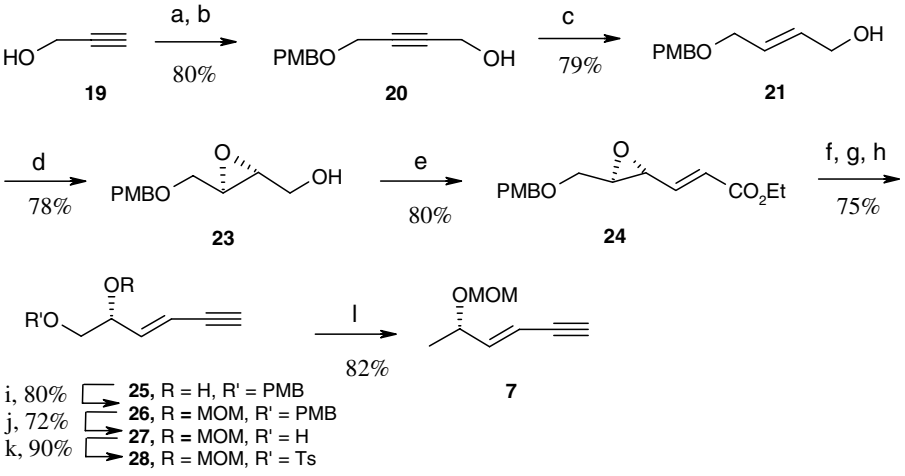
Scheme 5. Reagents and conditions: (a) $TiCl_4$ (0.01 equiv), DCM, 0 °C to rt, 2 h; (b) TsCl, pyridine, Et_3N, 0 °C, 45 min; (c) MOMCl (5 equiv), DIPEA (6 equiv), DCM, 0 °C to rt, 3 h; (d) LAH (1 equiv), ether, 0 °C to rt, 45 min; (e) $NH_2OH{\cdot}HCl$ (1 equiv), $EtNH_2$ (1 equiv), CuCl (0.2 equiv), MeOH, H_2O, 20 min; (f) 6 N HCl, 0 °C to rt, 2 h.

in 70% yield. Finally, removal of the MOM group provided the second target molecule, (*S*)-minquartynoic acid (**2**) in 78% yield (Scheme 5). The spectral data of **2** was in accordance with the natural product.

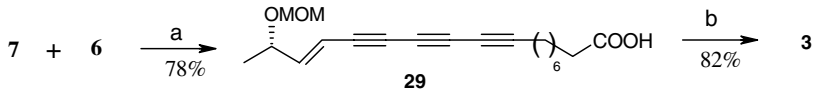
Next, (*E*)-15,16-dihydrominquartynoic acid (**3**) was synthesized using a different strategy starting from commercially available propargyl alcohol, as illustrated in Scheme 6. Protection of the hydroxyl group in **19** using PMBBr and NaH in dry THF at 0 °C resulted in the corresponding PMB ether, which on reaction with the Grignard reagent generated from EtBr and Mg, followed by quenching with *para*-formaldehyde furnished the propargyl alcohol derivative **20** in an overall yield of 80%. Compound **20** was then converted into *trans*-allylic alcohol **21** in 79% yield by the reduction of the triple bond using LAH in dry THF for 4 h. Alcohol **21** was then converted to monoprotected enyne **7**, as previously reported.[11]

The coupling reaction of *trans*-enyne **7** with bromodiyne **6** under Cadiot–Chodkiewicz reaction conditions afforded enetriyne **29**, which on removal of the MOM group provided the target molecule (*E*)-15,16-dihydrominquartynoic acid (**3**) in 82% yield (Scheme 7). The data for the synthetic material was identical to the natural product in all respects.

In summary, we have accomplished the total syntheses of the highly potent anti-cancer agents, (*S*)-18-hydroxyminquartynoic acid, (*S*)-minquartynoic acid and (*E*)-15,16-dihydrominquartynoic acid[16] using the Cadiot–Chodkiewicz cross-coupling reaction as the key step.



Scheme 6. Reagents and conditions: (a) NaH (1 equiv), PMBBr (1 equiv), THF, 0 °C to rt, 6 h; (b) EtMgBr (1.5 equiv), HCHO (1 equiv) 0 °C to rt, 4 h; (c) LAH (0.5 equiv), THF, 0 °C to rt, 4 h; (d) (+)-DIPT (0.3 equiv), $Ti(OiPr)_4$ (0.3 equiv), 4 Å MS, *t*-BuOOH (1.2 equiv), −25 °C, DCM, 4 h; (e) 1. $(COCl)_2$, DMSO, TEA, DCM, 45 min; 2. $Ph_3P{=}CHCO_2Et$, benzene, 0 °C to rt, 4 h; (f) DIBAL-H (1 equiv), −10 °C to rt, 1 h; (g) TPP (1 equiv), CCl_4, reflux, 4 h; (h) LDA (3 equiv), HMPA:THF (1:5 equiv), −78 °C, 1 h; (i) MOMCl (5 equiv), DIPEA (6 equiv), DCM, 0 °C to rt, 4 h; (j) DDQ (1.2 equiv), DCM/H_2O (9:1), 30 min; (k) TsCl (1 equiv), Et_3N, 0 °C, 1 h; (l) LAH (1 equiv), ether, 0 °C to rt, 30 min.



Scheme 7. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$ (1 equiv), $EtNH_2$ (1 equiv), CuCl (0.2 equiv), MeOH, H_2O, 20 min; (b) 6 N HCl, 0 °C to rt, 2 h.

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16. Selected spectral data: (*S*)-18-Hydroxyminquartynoic acid (**1**): solid, mp 96 °C (lit.[4] mp 95 °C); $[\alpha]_D$ −40.0 (*c* 0.50, MeOH); lit.[4] $[\alpha]_D$ −38.4 (*c* 0.1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30–1.60 (m, 10H), 2.26 (m, 4H) 3.56 (d, $J = 6.7$ Hz, 2H), 4.50 (t, $J = 7.3$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.1, 81.8, 78.0, 70.1, 65.4, 64.3, 62.9, 62.5, 58.9, 33.7, 30.1, 29.6, 29.1, 28.9, 28.8, 28.6, 25.6, 19.1; IR (neat): 3415, 2932, 2485, 2280, 2215, 1616, 1512, 1104 cm^{-1}; LCMS: *m*/*z* 323.12. ($M = 323.1 = M^+ + 23$ i.e., Na).
(*S*)-(−)-Minquartynoic acid (**2**): solid, mp 132–135 °C (lit.[4] mp 130–135 °C); $[\alpha]_D$ −31.0 (*c* 0.50, MeOH); lit.[4] $[\alpha]_D$ −29.4 (*c* 0.1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30–1.60 (m, 13H), 2.26 (m, 4H), 4.58 (q, $J = 6.7$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.0, 81.2, 80.8, 67.5, 65.0, 63.3, 62.7, 59.8, 57.3, 34.1, 29.1, 29.0, 28.8, 28.6, 28.0, 25.1, 23.7, 19.1; IR (neat): 3416, 2930, 1715, 1617, 1410, 1217, 1090 cm^{-1}; LCMS: *m*/*z* 307.12 ($M = 307.12 = M^+ + 23$ i.e., Na).
(*E*)-15,16-dihydrominquartynoic acid (**3**): amorphous solid, mp 50–52 °C (lit.[10] mp 49–52 °C); $[\alpha]_D$ −12.6 (*c* 0.50, MeOH); lit.[4] $[\alpha]_D$ −12.9 (*c* 0.1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24–1.67 (m, 13H), 2.33 (m, 4H), 4.34 (m, 1H), 5.73 (d, $J = 15.8$ Hz, 1H), 6.37 (dd, $J = 5.3$, 15.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.2, 151.4, 107.3, 82.7, 76.0, 74.4, 68.4, 67.5, 66.2, 59.8, 57.3, 34, 29.3, 29.6, 28.79, 24.5, 22.8, 19.7; IR (neat): 3416, 2930, 2395, 2260, 1617, 1560, 1143, 1030, 886 cm^{-1}; LCMS: *m*/*z* 309.4 ($M = 309.2 = M^+ + 23$ i.e., Na).